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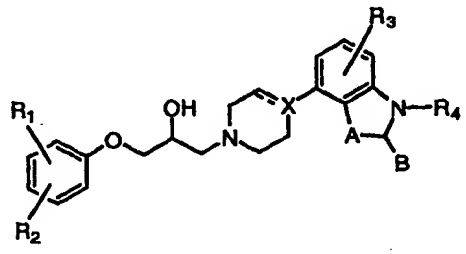

(1)

(57) Abstract

The present invention provides novel compounds of general formula (1), wherein R_1 and R_2 are H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, OR_5, nitro, amino, CF_3 or R_1 and R_2 are taken together to form a fused ring at the 1,2– or 2,3–positions providing a fused phenyl group or a benzodioxane group, or a 4– or 7–substituted indole group, or a 4– or 5– or 8–substituted quinoline group; R_3 represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen; R_4 represents a group selected from hydrogen, 1 to 6 carbon alkyl or R_5; R_5 is CH_2Ph in which the phenyl ring can be optionally substituted by a group selected from OMe, halogen, CF_3; X is selected from a group represented by N, CR_4, CHR_4 and CHCH; A is selected from a group represented by N, NH, CH and CH_2; B is selected from a group represented by =O, =S, H and H2; or A and B may be concatenated together to form indole, benzimidazole, indolone or indoline moieties; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions and methods of treating central nervous system disorders utilizing these compounds.

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ANTIPSYCHOTIC INDOLYL DERIVATIVES

This application claims the benefit of U.S. Provisional Application No. 60/104,596, which was converted from U.S. Patent Application No. 09/069,129, filed April 29, 1998, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

This invention concerns a series of novel β-hydroxy aryloxypropylamines which are effective pharmaceuticals for the treatment of conditions related to or affected by the dopamine D2 receptor and also by the serotonin 1A receptor subtype. The compounds are particularly useful for the treatment of schizophrenia and related psychotic disorders and other conditions such as Parkinson's disease and Alzheimer's disease.

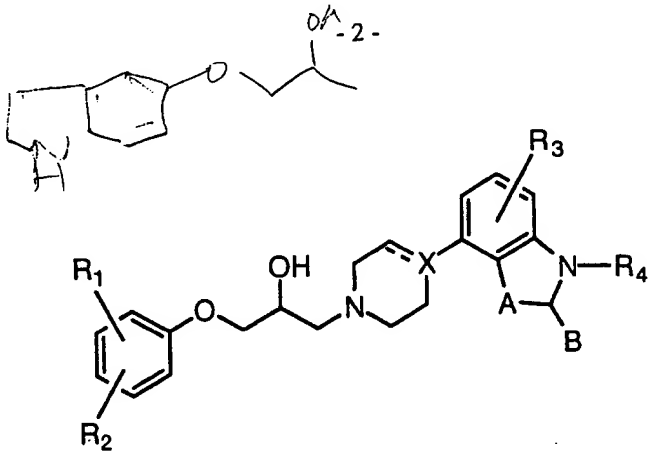
Background to the Invention

In their letter to the editor, TINS, Vol. 17, No. 4, 1994, Bowen et al. note that the cognitive impairment characteristics of Alzheimer's disease may be ameliorated by antagonists at the inhibitory 5-HT_{1A} receoptor, or by activation of the phospholipase-C-linked cholinergic M_1 receptor.

Summary of the Present Invention

This invention relates to novel indolyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy. The compounds are useful for the treatment of psychotic disorders, particularly schizophrenia. by virtue of their ability to antagonize the dopamine D2 receptor. Furthermore. the present invention also provides compounds that are antagonists and agonists at the 5-HT1A receptor subtype and thus compounds of this invention may be used to treat Alzheimer's Disease, Parkinson's Disease, depression and anxiety.

Compounds of the present invention are represented by the general formula (I),



(I)

wherein

R_1 and R_2 are each independently selected from H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, arylalkyl, aralkyloxy, OR_5, nitro, amino, CF_3 and when R_1 and R_2 are taken together, form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group, the substituents on the indole or quinoline groups being selected from from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S-C_1-C_6 alkyl, -CN, -OH, $-NO_2$ or $-CF_3$;

R_3 represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen;

R_4 represents a group selected from hydrogen, 1 to 6 carbon alkyl or R_5;

R_5 is CH_2Ph in which the phenyl ring can be optionally substituted by a group selected from OMe, halogen, CF_3;

X is selected from a group represented by N, CR_4, CR_4 and CHCH;

A is selected from a group represented by N, NH, CH and CH_2;

B is selected from a group represented by =O, =S, H and H2;

or A and B may be concatenated together to form indole, benzimidazole, indolone or indoline moieties;

or a pharmaceutically acceptable salt thereof.

It will be understood that the type of substitution indicated by B in the generic groups herein will be controlled by whether A is N, NH, CH or CH_2.

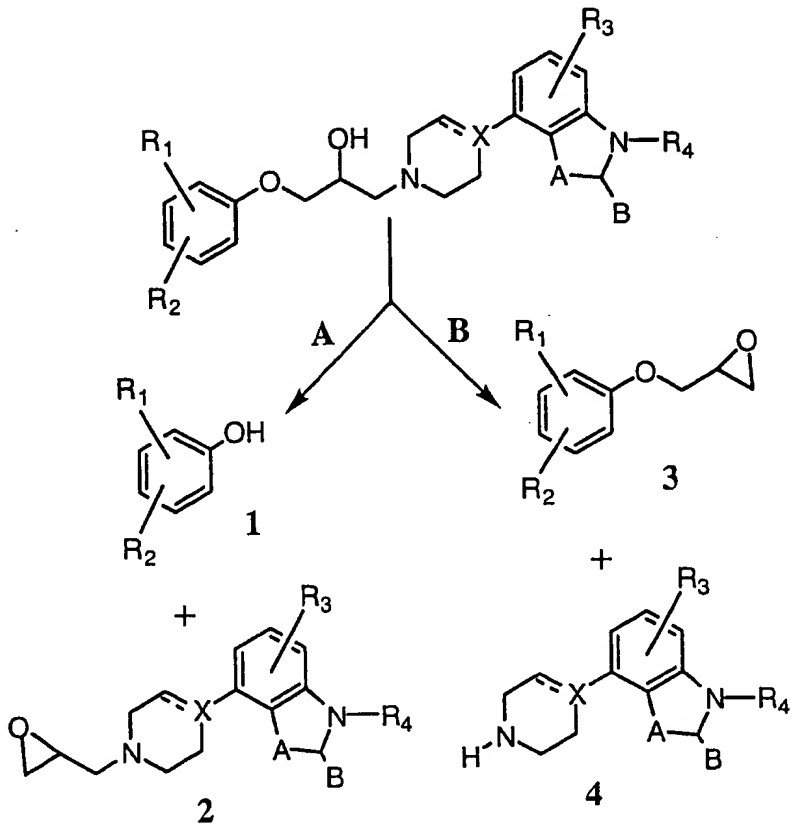
The term "aryl" as used in the definitions of R_1 and R_2 indicates phenyl, or pyridine groups, optionally substituted by from 1 to 3 substitutents selected from

halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S-C_1-C_6 alkyl, -CN, -OH, $-NO_2$ or $-CF_3$. The most preferred aryl group is phenyl, optionally substituted as just described. The most preferred arylalyl group in the definitions above is benzyl and the preferred aralkyloxy group is benzyloxy.

The pharmaceutically acceptable salts are the acid addition salts which can be formed from a compound of the above general formula and a pharmaceutically acceptable inorganic acid such as phosphoric, sulfuric, hydrochloric, hydrobromic citric, maleic, fumaric, acetic, lactic or methanesulfonic acid.

Detailed Description of the Invention

Compounds of the present invention may be prepared using conventional methods, utilizing for example the disconnections shown in scheme A and scheme B below.



In scheme A, the phenol 1 is reacted with an epoxide of formula 2 to afford the required product. The starting phenol may be commercially available or can be readily obtained by those practiced in the art of organic synthesis. The epoxide 2 is available for example, from the reaction of an amine of formula 4 with optically active or racemic epichlorohydrin or glycidyl tosylate.

In scheme B, the epoxide 3 can be obtained from the reaction of a phenol of formula 1 with optically active or racemic epichlorohydrin or glycidyl tosylate. Reaction of this compound with an amine of formula 4 affords the required product. The product can then be used to form a pharmaceutically acceptable addition salt.

Compounds of the present invention bind with very high to the 5-HT1A receptor and the dopamine D2 receptor and consequently, they are useful for the

treatment of central nervous system disorders such as schizophrenia, depression, anxiety, including generalized anxiety, sleep disorders, sexual dysfunction, alcohol and cocaine addiction, and related problems in addition to the treatment of Alzheimer's disease, Parkinson's disease, obesity and migraine. The present compounds can also be used in regimens to increase cognition enhancement. This invention includes methods of treating in mammals each of these maladies, as well as a method of increasing cognition enhancement, the methods comprising administering to a mammal in need thereof an effective amount of one or more of the compounds of this invention, or a pharmaceutically acceptable salt thereof.

It is understood that the therapeutically effective dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. Variables involved include the specific psychosis or state of anxiety and the size, age and response pattern of the patient. The novel method of the invention for treating conditions related to or are affected by the reuptake of serotonin comprise administering to warm-blooded animals, including humans, an effective amount of at least one compound of this invention or a non-toxic, pharmaceutically acceptable addition salt thereof. The compounds may be administered orally, rectally, parenterally. or topically to the skin and mucosa. The usual daily dose is depending on the specific compound, method of treatment and condition treated. An effective dose of 0.01 - 1000mg/Kg may be used for oral application, preferably 0.5 - 500 mg/Kg, and an effective amount of 0.1 - 100 mg/Kg may be used for parenteral application, preferably 0.5 - 50 mg/Kg.

The present invention also includes pharmaceutical compositions containing a compound of this invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

Applicable solid carriers or excipients can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintergrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of

the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions. for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself. or it can be the appropriate number of any such compositions in package form.

The affinity of drugs for the dopamine receptor was established by testing the claimed compound's ability to displace [^{3}H]-Spiperone binding in CHO cells stabily transfected with the human dopamine D2 receptor. CHO cells expressing the human dopamine D2 receptor were cultured in suspension by expansion (every 3 - 4 days) in a serum free media to provide approximately 7.5 x 10^5 cells/ml. The cells were harvested by centrifugation (900 x g for 10 min.), resuspended in half volume of 1X dulbecco PBS solution at pH 7.4, and after a further recentrifugation, the cell pellet was resuspended in 50 mM Tris.HCl (pH 7.4) containing 1.5 mM $CaCl_2$, 5.0 mM EDTA, 5.0 mM KCl, 120 mM NaCl, 1.0 mM PMSF and 1.0 mg % leupeptin. The cells were homogenized, centrifuged at 40,000 x g for 30 minutes and resuspended in fresh buffer (10 ml), and the process repeated twice. The final pellet was suspended in a volume of 50.0 mM Tris.HCl sufficient to give a protein concentration of 125.0 µg/ml of membrane suspension. The binding assay is performed in a 96 well microtiter plate. 100 µl of buffer is added to the wells, and those receiving a displacer for nonspecific binding (NSB) assessment or test compounds receive 80 µl of incubation buffer. [3H]-Spiperone (S.A. 89 - 100 Ci/mmole) is used as ligand and 0.5 nM in 20 µl volume is added to all wells, followed by the addition of the displacer D-butaclamol (1µM in 20 µl) for nonspecific binding determination. The reaction is initiated by the addition of 80 µl of the tissue membrane, and after 120 minutes at room temperature the wells are harvested using a Brandell® Harvester onto glass fiber filter presoaked in 0.1% polyethylimine. After washing three times with cold 50 mM Tris.HCl, the filter mat is oven dried and sealed in an envelope with melted multitex for scintillation counting in a Wallac 1205 BetaPlate Counter. The data is analyzed and Ki values are computed for active compounds. Using this assay, the following Ki's were determined for a series of standard D2 receptor ligands.

Compound	**D2 binding Ki (nM)**
Spiperone	0.08
Clozapine	28.6
Haloperidol	0.57
7-OHDPAT	96
Sulpiride	49.4

The results for a number of examples of compounds of formula 1 in this standard experimental test procedure were as follows

Compound	D2 binding Ki (nM)
Example 2	33.5
Example 5	31.9
Example 6	10.4

High affinity for the serotonin 5-HT_{1A} receptor was established by testing the claimed compound's ability to displace [^{3}H] 8-OH-DPAT binding in CHO cells stably transfected with human 5HT1A receptor. Stably transfected CHO cells are grown in DMEM containing 10% heat inactivated FBS and non-essential amino acids. Cells are scraped off the plate, transferred to centrifuge tubes, and washed twice by centrifugation (2000 rpm for 10 min., 4°C) in buffer (50 mM Tris pH 7.5). The resulting pellets are aliquoted and placed at -80°C. On the day of assay, the cells are thawed on ice and resuspended in buffer. The binding assay is performed in a 96 well microtiter plate in a total volume of 250 µL. Non-specific binding is determined in the presence of 10 mM 5HT, final ligand concentration is 1.5 nM. Following a 30 minute incubation at room temperature, the reaction is terminated by the addition of ice cold buffer and rapid filtration through a GF/B filter presoaked for 30 minutes in 0.5% PEI. Compounds are initially tested in a single point assay to determine percent inhibition at 1, 0.1, and 0.01 mM, and Ki values are determined for the active compounds.

Compound	5-HT1A binding Ki (nM)
Example 1	6.0
Example 2	7.6
Example 3	1.8
Example 4	8.8
Example 5	12.1
Example 6	10.4
Example 7	7.2
Example 8	4.5

The following non-limiting specific examples are included to illustrate the synthetic procedures used for preparing compounds of the formula 1. In these examples, all chemicals and intermediates are either commercially available or can be prepared by standard procedures found in the literature or are known to those skilled in the art of organic synthesis.

Example 1

1-(1H-Indol-4-yloxy)-3-[4-(1H-indol-4-yl) piperazin-1-yll-propan-2-ol

A methanolic solution (20 ml) of 1-(indole-4-oxy)-2,3-epoxypropane (0.38 g, 2.0 mmole) was added dropwise under a nitrogen atmosphere to a stirred solution of 1-(indol-4-yl)-piperazine (0.4 g, 2.0 mmole) in methanol (75 ml). The mixture was heated to reflux for 2 hrs, concentrated in vacuo, and the product purified by column chromatography over silica gel (CH_2Cl_2:MeOH 95:5) to afford an oil (0.7g, 90% yield). Treatment with a 0.25M ethanolic fumaric acid solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 147-150°C

Elemental Analysis for: C23H26N4O2. 1.0C4H4O4

Calculated: C. 64.02; H, 5.97; N, 11.06

Found: C, 64.59; H, 6.36; N, 11.81

Example 2

1-(4-Chloro-phenoxy)-3-[4-(1H-indol-4-yl) piperazin-1-yll-propan-2-ol

A methanolic solution (75 ml) of 4-chlorophenyl-2,3-epoxypropyl ether (0.55 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc:Hexane 90:10) to afford a white solid (1.25 g. 100%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 224-225°C

Elemental Analysis for: C21H24ClN3O2. 0.5C4H4O4

Calculated: C. 62.23; H, 5.9; N, 9.47

Found: C, 61.98; H, 5.79; N, 9.21

Example 3

1-[4-(1H-Indol-4-yl)-piperazin-1-yll-3-(4-methoxy-phenoxy)-propan-2-ol

A methanolic solution (75 ml) of 4-methoxyphenyl-2,3-epoxypropyl ether (0.54 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH_2Cl_2:MeOH 90:10) to afford a white solid (1.1 g. 96%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 226-227°C

Elemental Analysis for: C22H27N3O3. 0.5C4H4O4

Calculated: C. 65.59; H, 6.65; N, 9.56

Found: C, 65.36; H, 6.48; N, 9.36

Example 4

1-[4-(1H-Indol-4-yl)-piperazin-1-yll-3-(4-nitro-phenoxy)-propan-2-ol

A methanolic solution (65 ml) of 1,2-epoxy-3-(4-nitrophenoxy)-propane (0.59 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo to afford the product as a yellow solid (1.1 g, 93%). Treatment with a 4M etheral HCl solution gave the required product, which was recrystallized from ethanol to afford the title compound as a light yellow solid.

m.p. 248°C

Elemental Analysis for: C21H24N4O4. 1.0HCl

Calculated: C, 58.26; H, 5.82; N, 12.94

Found: C, 57.92; H, 5.76; N, 12.66

Example 5

1-(2-Chloro-phenoxy)-3-[4-(1H-indol-4-yl) piperazin-1-yll-propan-2-ol

A methanolic solution (75 ml) of 1-(2-chlorophenoxy)-2,3-epoxypropane (0.55 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH_2Cl_2:MeOH 90:10) to afford a white solid (1.09 g, 94%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 207°C

Elemental Analysis for: C21H24ClN3O2. 0.5C4H4O4

Calculated: C, 62.23; H, 5.9; N, 9.47

Found: C, 62.13; H, 5.72; N, 9.34

Example 6

1-(4-Fluoro-phenoxy)-3-[4-(1H-indol-4-yl) piperazin-1-yl]-propan-2-ol

A methanolic solution (50 ml) of 1-(4-fluorophenoxy)-2,3-epoxypropane (0.50 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc) to afford a white solid (1.1 g, 99%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required salt, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 234-235°C

Elemental Analysis for: $C_{21}H_{24}FN_3O_2 . 0.5C_4H_4O_4$

Calculated: C, 64.62; H, 6.13; N, 9.83

Found: C, 64.38; H, 6.01; N, 9.67

Example 7

4-{2-Hydroxy-3-[4-(1H-indol-4-yl)-piperazin-1-yl] propoxy}-1H-indole-2-carboxylic acid amide

A methanolic solution (50 ml) of 1-(2-carboxamidoindol-4-oxy)-2,3-epoxypropane (0.83 g, 1.5 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 0.5 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH_2Cl_2:MeOH 90:10) to afford a white solid (1.24 g, 97%). Treatment with a 1.0M etheral HCl solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 258-259°C

Elemental Analysis for: $C_{24}H_{27}N_5O_3 . 1.0HCl$

Calculated: C. 60.5; H, 6.08; N, 14.7

Found: C, 60.31; H, 5.89; N, 14.6

Example 8

1-(Biphenyl-2-yloxy)-3-[4-(1H-indol-4-yl) piperazin-1-yl]-propan-2-ol

A methanolic solution (50 ml) of 2-biphenylglycidyl ether (0.68 g, 1.5 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 15 hrs under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc) to afford a white solid (1.23 g, 96%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required salt, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 214-215^{0}C

Elemental Analysis for: C27H29N3O2. 1.0C4H4O4

Calculated: C, 68.49; H, 6.12; N, 7.73

Found: C, 68.6; H, 6.12; N, 7.88

Example 9

1-(1H-Indol-4-yloxy)-3-[4-(1H-benzimidazole-4-yl) piperazin-1-yl]-propan-2-ol

The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-benzimidazole-4-yl)piperazine (2 mmole) according to the above procedures.

Example 10

1-(1H-Indol-4-yloxy)-3-[4-(1H-2,3-dihydroindol-4-yl) piperazin-1-yl]-propan-2-ol

The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-2,3-dihydroindol-4-yl)piperazine (2 mmole) using the procedures outlined in the previous examples.

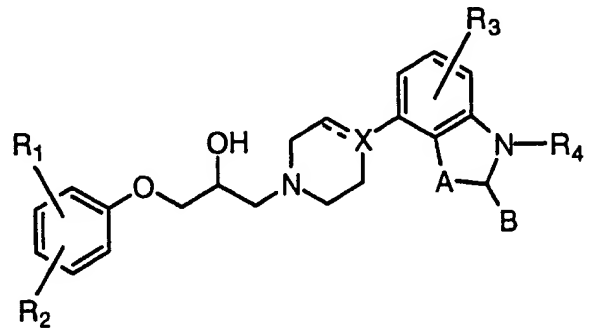
Example 11

1-(1H-Indol-4-yloxy)-3-[4-(1H-2-oxindol-4-yl) piperazin-1-yl]-propan-2-ol

The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-2-oxindol-4-yl)piperazine (2 mmole) using the procedures outlined in the previous examples.

We claim:

1. A compound according to the formula;



wherein

R_1 and R_2 are each independently selected from H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, arylalkyl, aralkyloxy, OR_5, nitro, amino, CF_3 and when R_1 and R_2 are taken together, form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group, the substituents on the indole or quinoline groups being selected from from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -S-C_1-C_6 alkyl, -CN, -OH, $-NO_2$ or $-CF_3$;

or R_1 and R_2 are taken together, form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group;

R_3 represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen;

R_4 represents a group selected from hydrogen, 1 to 6 carbon alkyl or R_5;

R_5 is CH_2Ph in which the phenyl ring can be optionally substituted by a group selected from OMe, halogen, CF_3;

X is selected from a group represented by N, CR_4, CR_4 and CHCH;

A is selected from a group represented by N, NH, CH and CH_2;

B is selected from a group represented by =O, =S, H and H2;

or A and B may be concatenated together to form indole, benzimidazole, indolone or indoline moieties;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 which is 1-(1H-indol-4-yloxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 which is 1-(4-chloro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 which is 1-[4-(1H-indol-4-yl)-piperazin-1-yl]-3-(4-methoxy-phenoxy)-propan-2-ol

5. A compound of claim 1 which is 1-[4-(1H-indol-4-yl)-piperazin-1-yl]-3-(4-nitro-phenoxy)-propan-2-ol or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1 which is 1-(2-chloro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1 which is 1-(4-fluoro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

8. A compound of claim 1 which is 4-{2-hydroxy-3-[4-(1H-indol-4-yl)-piperazin-1-yl]propoxy}-1H-indole-2-carboxylic acid amide or a pharmaceutically acceptable salt thereof.

9. A compound of claim 1 which is 1-(biphenyl-2-yloxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

10 A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-benzimidazole-4-yl)piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

11. A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-2,3-dihydroindol-4-yl) piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

12. A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-2-oxindol-4-yl) piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

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14. A method for treating schizophrenia in a mammal, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.